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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,586	12/20/2001	Vanessa Chisholm	P1746R1	1705

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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,586	CHISHOLM ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-34,36-54,56-58 and 102-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *8-16,34,36,45,49-54,56-58 and 102-105* is/are allowed.

6)☒ Claim(s) *1-6,17-33,37-44 and 46-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *May/Oct 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response, filed 03/08/2005, canceling claim 55, amending claims 1-6, 8-34, 36-41, 44, 46-47, 49-50, 53-54, 56-57 and 102-103, and adding new claims 104-105. Claims 1-6, 8-34, 36-54, 56-58 and 102-105 are currently pending and under consideration in this action. All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections/rejections repeated herein. As no new grounds of rejection are set forth herein that were not necessitated by material changes to the claims, **this action is made FINAL**.

Information Disclosure Statement

The information disclosure statement filed 10/21/2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because a listed reference is in a foreign language, with no English translation provided (i.e., EP 0711835 A). It has been placed in the application file, but the information referred to therein, which has been crossed through, has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶C (1).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 17-33 and 37-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

This is a new ground of rejection that is necessitated by material changes to the claims. Independent claim 17 recites the term "the GFP" which does not find sufficient antecedent support.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. **Claims 1-6, 39-44 and 46 rejected under 35 U.S.C. 103(a) as being unpatentable over Tan et al. (US 6,235,967; see whole document; hereinafter the '967 patent; reference of record) as applied to or further in view of Chishima et al. (Cancer Res. 1997; 57:2042-47; reference of record).**

This rejection was made previously and is repeated herein. A response to Applicant's argument is set forth immediately following the body of this rejection. The rejection as to claims 8-9 is withdrawn.

The claims are drawn to a polynucleotide comprising an amplifiable gene, a green fluorescent protein (GFP) and a selected sequence encoding a desired product (i.e. target gene), where the target gene is operably linked to either the amplifiable gene or to GFP and to a promoter. The limitation, operably linked is interpreted as broadly as reasonable, to include the interpretation that nucleic acids are linked in some fashion so as to confer a functional objective (e.g. amplification or propagation of a vector in bacteria). Furthermore, the claims are directed to the amplifiable gene encoding DHFR and the GFP is further limited to mutant GFP – S65T. The invention is further directed to cells and a kit comprising the polynucleotide with the aforementioned characteristics. In addition, the limitation for a kit is interpreted as broadly as reasonable to mean any container comprising the polynucleotides of the invention.

The '967 patent teaches a polynucleotide where GFP is fused to a selected sequence (e.g. methioninase or T antigen) and operably linked to a promoter. (e.g. Abstract; Fig. 1a). Further, GFP can be of a higher fluorescence mutated (i.e. S65T) variety. (e.g. col. 3, l. 26). In addition, various cell types can be transfected with the polynucleotide, including methotrexate selected CHO cells. (e.g. col. 3, line 63; col. 6, ll. 27-37).

Furthermore, the '967 indicates using a DHFR-GFP dicistronic vector (e.g. col. 6, Example 1; showing GFP-S65T mobilization into pED-mtx^r) and explicitly teaches that such vector systems can be used to express proteins in mammalian cells. (e.g. col. 9, ll. 40-45). In addition, the polynucleotides would necessarily be contained in a container (e.g. eppendorf tubes), which constitutes a kit. The '967 patent doesn't expressly provide a construct where a target gene is operably linked to either a gene encoding GFP or a gene encoding an amplifiable selectable marker, where the construct comprises both genes regardless.

However, in essence, the '967 patent all but reduces to practice what is missing. For example, a GFP-target fusion is taught with a selection marker. (e.g. Fig. 1a). Furthermore, the '967 patent teaches that a dicistronic vector comprising both a fluorescence encoding gene (i.e. GFP) and an amplifiable selectable marker (i.e. DHFR) can be used. (e.g. col. 9, ll. 40-45). In addition, the '967 patent teaches that said polynucleotides can be used for production of a fusion protein (e.g. GFP-T antigen). (e.g. col. 9, ll. 50-51). Therefore, the '967 patent provides the motivation to construct a vector comprising a gene encoding a fluorescence marker, an amplifiable selectable marker and a target protein.

In addition, Chishima et al. teach an expression construct where a GFP gene (S65T) is mobilized into a dicistronic expression vector comprising an amplifiable gene (i.e. DHFR) and a gene expressing a desired product. (Chishima, at 2042, col. 2, ¶3, referring to the pED-mtx^r construct described in, Kaufman et al. Nucleic Acids Research. 1991; 19(16):4485-90) (Note: this second reference is only being cited to provide information with regard to intrinsic properties of the pED-mtx^r expression construct not as additional art, See MPEP § 2131.01).

Kaufman et al. teach that the pED-mtx^r construct contains a gene encoding a desired product operably linked to a promoter (i.e. B-lactamase gene, Kaufman, at 4487, Fig. 1). Chishima et al. further teach that the construct replicates in CHO cells. (Chishima, at 2042, col. 2, ¶4). Therefore, it would have been well within the knowledge of one of ordinary skill to construct the expression vector to produce the GFP fusion proteins as contemplated by the '967 patent. The ordinary skilled artisan, seeking to develop a construct for expressing proteins that can be easily be monitored via fluorescence and that can be selected for in mammalian cells via amplifiable markers such as DHFR, would have been motivated to incorporate the teachings of the '967 patent or Chishima et al. to construct a expression construct comprising GFP, a selected sequence and DHFR, operably linked to a promoter. It would have been obvious for the ordinary skilled artisan to so construct an expression vector and transfect mammalian cells to express the desired fusion proteins. Furthermore, given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said artisan would have had a reasonable expectation of success in practicing the claimed invention.

Response to Arguments

Applicant's arguments have been fully considered and is deemed persuasive as to claims 8 and 9, but is not deemed persuasive as to the remaining rejected claims. In sum, Applicant asserts that the cited prior art does not teach nor suggest the claimed invention and that there was no reasonable expectation of success. (Remarks, p. 15). Furthermore, Applicant asserts that regarding claims 8 and 9, the cited art does not teach or suggest a GFP-amplifiable selectable marker fusion operably linked to a promoter. (Remarks, p. 17)

Moreover, Applicant asserts that the limitation "operably linked" is explicitly defined in the specification, whereby said definition should control claim interpretation. (e.g., Remarks, p. 15, middle). Since claim interpretation with respect to the limitation "operably linked" underpins the grounds of rejection and Applicant's rebuttal arguments, it will be discussed first.

It may be true that a definition is provided in the specification with respect to the term "operably linked". (Specification, p. 18, top). However, the definition provided is quite broad and does not limit to any significant degree how the term "operably linked" should be interpreted. The specification provides the following definition:

> "Operably linked" refers to a juxtaposition of two or more components, wherein the components so described are in a relationship permitting them to function in their intended manner. For example, a promoter and/or enhancer is operably linked to a coding sequence if it acts in cis to control or modulate the transcription of the linked sequence. Generally, but not necessarily, the DNA sequences that are "operably linked" are contiguous and, where necessary to join two protein coding regions or in the case of a secretory leader, contiguous in reading frame. However, although an operably linked promoter is generally located upstream of the coding sequence, it is not necessarily contiguous with it. (Specification, p. 18, ll. 1-8).

The definition provided is controlling insofar as any reasonable interpretation can be made with respect to the limitation "operably linked". As the specification teaches, the components or elements comprising the vector do not have to be related in a contiguous manner. Furthermore, the requirement that the components are in a relationship permitting the components to function in their intended is quite broad. For example, where several components are on the same plasmid or vector, and each component is "in a relationship permitting them to function...", literally encompasses any combination/positioning of the components on the vector. Therefore, the broadest reasonable interpretation would encompass a vector where components occur in any order, at least regarding the broadest claims.

As stated in the rejection, the '967 patent teaches mobilization of GFP-S65T into the plasmid pED-mtx^r. (col. 6, ll. 14-26). Further, as Kaufman et al. teaches through illustration of a schematic for pED-mtx^r, the mobilization of said GFP would result in a vector that comprises a polynucleotide encoding GFP operably linked to a polynucleotide encoding DHFR. (Supra, Kaufman et al. 1991, p. 4486, col. 1, last ¶; p. 4487, Figure 1). Furthermore, a polynucleotide encoding a desired product (i.e., β-lactamase) is comprised on the same vector and said β-lactamase is certainly within the definition provided in the specification, i.e., "in a relationship permitting... [it] to function...". (Ibid, Specification, p. 18).

Moreover, regarding motivation to modify the vector, the '967 patent teaches that the vector *is* modified (i.e., GFP inserted into the pED-mtx^r plasmid), thus provides the necessary modification explicitly. Furthermore, the DHFR and GFP components are function as demonstrated by the '967 patent. (col. 6, ll. 26-46; indicating transfected clones are selected via methotrexate selection and high intensity GFP fluorescence). Therefore, there is a clear demonstration of success in constructing the vector that meets the claimed limitations. In view of the reasonable interpretation of the limitation "operably linked", given the level of skill of the artisan and given the utilization of the dicistronic vector as taught by the '967 patent, there was a demonstrable showing of success. In sum, the rejected claims are obvious over the cited art.

3. **Claims 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tan et al. (US 6,235,967) or Chishima et al. (Cancer Res. 1997; 57:2042-47), and further in view of Moir and Mao (Bioprocess Technol. 1990; 9:67-94; reference of record) or Lubiniecki et al. (Biologicals. 1994, 22(2): 161-9; reference of record).**

This rejection was made previously and is repeated herein. A response to Applicant's argument is set forth immediately following the body of this rejection. The '967 patent or Chishima et al. do not explicitly indicate that proteins expressed can be recovered or recovered from culture.

Moir and Mao teach that proteins of interest can be produced and targeted to different compartment of cells within which they are produced or secreted into the culture medium using secretory pathways of yeast and mammalian cells. (See e.g. p. 67, ¶1). Moir and Mao explicitly state that protein products from exogenously added genes on recombinant vectors can be targeted to the culture medium for production (i.e. recovery) of industrially important proteins. (Id., ¶¶ 1-3). Furthermore, Lubiniecki and Lupker teach that recombinant proteins produced in an animal cell culture system can be purified using chromatography techniques known in the art to medicinal quality. (p. 167, ¶ 3).

The ordinary skilled artisan seeking to produce proteins for biotechnology or pharmaceutical applications in cell culture systems would have been motivated to combine the teachings of the '967 patent or Chishima et al. – an expression system designed to express proteins of interest in addition to sorting via fluorescence – with the teachings of Moir and Moi or Lubiniecki and Lupker – using cell culture systems combined with standard chromatography techniques to purify (i.e. recover) proteins of interest, with the added benefit of FACS sorting. Therefore it would have been obvious for the ordinary skilled artisan to incorporate the '967 patent's selection/expression system to express proteins that could then be purified or recovered.

Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of applicant's invention, it must be considered that the skilled artisan would have had a reasonable expectation of success in expressing a target protein to be recovered from a cell culture system using the '967 patent's dicistronic selection/expression system.

Response to Arguments

Applicant has not presented any arguments independent of the arguments presented above, regarding Tan et al. and Chishima et al. Therefore, because the arguments regarding Tan et al. and Chishima et al. are not deemed persuasive, this rejection is also maintained.

Allowable Subject Matter

Claims 8-16, 34, 36, 45, 49-54, 56-58 and 102-105 are allowed.

Conclusion

Claims 1-6, 17-33, 37-44 and 46-48 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636